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(54) PROCESS FOR ENCAPSULATING ASPIRIN

(71) We, FUJI PHOTO FILM CO., LTD., a Japanese Company, of No. 210, Nakanuma, Minami/Ashigara-Shi, Kanagawa, Japan, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a process for the encapsulation of aspirin with a cellulose derivative: in the process water containing an organic solvent partially miscible with water and/or a small amount of aspirin is used as the encapsulation medium.

Processes for producing cellulose capsules containing aspirin are known. For example, there is known a method utilizing the phase separation of ethyl cellulose and polyethylene by heating and cooling a solution thereof in a pure organic solvent such as cyclohexane. Such a method is attended by the danger inherent in the requirement to heat cyclohexane to temperatures near its boiling point during phase separation, and the necessity for a complicated operation to separate polyethylene by filtration.

There is also known a process for producing such capsules utilizing the phase separation of a concentrated aqueous salt solution and acetone. However, in this process salt adhering to the walls of the capsules so formed must be washed away with water thus constituting an additional troublesome operation.

Each of the above processes poses technical problems which should desirably be solved to achieve a really acceptible encapsulation technique for aspirin.

Accordingly, one object of the present invention is to provide a process for producing aspirin-containing capsules in an aqueous medium easily and efficiently and which is not accompanied by the above-mentioned defects of the prior art.

The above-mentioned object of the present invention can be attained by the process of the present invention which comprises:

1) dispersing aspirin particles in a solution of a film-forming cellulose derivative in an organic solvent partially miscible with water;

2) adding the dispersion to an encapsulation medium comprising water in which is dissolved an organic solvent which is partially miscible with water and/or aspirin;

3) stirring the mixture to form a fine dispersion of the aspirin; and

4) evaporating off the organic solvent thereby to encapsulate the aspirin particles in the cellulose derivative.

Details of some aspects of the process of the present invention will now be described below:

a) As the capsule wall-forming substance a cellulose derivative such as an alkyl cellulose, preferably ethyl cellulose, most preferably having an ethoxyl content of from 40.8 to 49.5% by weight is used. The term "cellulose derivative" means cellulose in which a hydrogen atom of at least one hydroxyl group of the cellulose molecule is substituted.

b) A solution of the cellulose derivative is prepared by dissolving it in an organic solvent, which is a solvent for the cellulose derivative and is partially miscible with water in an amount of at least about 1 wt. % i.e. at least 1 gram of the solvent must mix with 100 grams of water; the preferred maximum degree of miscibility is about 35 g per 100 grams of water. Then aspirin particles are dispersed in the solution to form a dispersion. Aspirin may be dissolved in the solution of the cellulose derivative, but it is preferred to choose an organic solvent that dissolves only a small amount of aspirin. The cellulose derivative on the other hand is completely dissolved by the organic solvent and the resultant solution preferably contains the cellulose derivative in an amount of from 1 to 10% by weight.

c) As the encapsulation medium, there is prepared one of the following: water having dissolved therein an amount of preferably

from 1 wt % to the almost saturated amount (see Table 1) of an organic solvent partially miscible with water (which may be the same as or different from the solvent(s) of step (2); water preferably having dissolved therein at least 0.01 wt % aspirin; or water containing the organic solvent and aspirin as described above. While the maximum amount of aspirin is not very important, the maximum amount of aspirin that can be dissolved in 100 g of water at 20°C is about 0.6 g. It is thus seen that the possible variation is relatively small.

d) The aspirin-containing dispersion prepared in step (2) is added to the aforesaid encapsulation medium maintained at any desired temperature preferably not higher than 25°C, more preferably at a temperature of not higher than 18°C, but above the freezing point thereof, and the mixture is stirred to divide the aspirin-containing dispersion into particles usually of a size of from 0.1 to 2 mm. By evaporating off the organic solvent while stirring, the cellulose derivative is deposited around the aspirin particles to form walls, whereby a great number of capsules containing aspirin are simultaneously prepared. The process is conveniently completed in 1 to 4 hours. The pressure used is preferably somewhat lower than atmospheric pressure e.g. 750 to 500 mm Hg. Excessively low pressures should be avoided as these may cause holes in the capsule walls. The solvent may be evaporated off, e.g. by stirring the solution containing the solvent, and additionally by blowing air thereagainst. It is preferred to employ a solvent having a boiling point no higher than 100°C and which is readily volatile.

The solvents which are used in step 1) of the process of the present invention are those which scarcely dissolve aspirin (having at most a dissolving power of 2 or 3 percent, which is negligible from the point of view of manufacturing capsules). Further, though it is unavoidable that a few percent of the aspirin is dissolved by the polymer solution and/or water (encapsulation medium) at the equilibrium state (concentration), this is also negligible from the point of view of manufacturing capsules.

It should also be noted that the form and size of the capsules can be effectively adjusted by previously adding to the water of the encapsulation medium used in step 2) solvent for the cellulose derivative in an amount up to saturation concentration used, since a rapid diffusion of the solvent from the cellulose derivative-containing solution to water is thereby prevented when that solution is incorporated in water in step 2).

According to the present invention, although the reason for this is unclear, the cellulose derivative is very effective for forming the capsule walls, neither solid beads nor crumbs of the cellulose derivative being formed.

In addition, by the process of the present invention capsules having a most preferred size, i.e. from 0.2 to 1 mm, may be obtained by controlling stirring and also a stable product of constant quality may also thereby be obtained. Moreover, the aspirin-containing capsules encapsulated by the cellulose derivative have long durability since aspirin is not dissolved out of the capsules and the evaporation of the organic solvent may be smoothly conducted during the encapsulation. Additionally, the decomposition of aspirin into salicylic acid hardly occurs.

After completion of encapsulation, the capsules are recovered from the aqueous medium by filtration and the remaining solvent may easily be removed from the capsules by a blast of warm air or by vacuum drying. The recovered encapsulation medium can be repeatedly used merely by supplementing fresh organic solvent.

Hhe materials which may be employed in the present invention will now be described in further detail.

It is desirable to use aspirin having a particle size of from 50 to 500 μ as listed in the Japanese Pharmacopoeia. As the cellulose derivative, ethyl cellulose having an ethylation degree of from about 47 to about 50%, which is commercially avaliable under the tradename "N-100" from Hercules Co. Ltd., is convenient for practical use, but the cellulose derivative is not necessarily limited thereto and persons skilled in the art will be able to select a suitable cellulose derivative.

Typical organic solvents partially miscible with water include alcohols, ethers, ketones and esters, which are exemplified in Table 1 below. From the viewpoint of the dissolution of the cellulose derivtives (especially ethyl cellulose) and aspirin, ease of evaporation, cost and ease of recovery, esters or mixtures of the solvents described above are preferred.

TABLE 1

Solvent	Boiling point (°C)	Amount dissolved in 100 g of water (temperature in °C in parentheses)
Alcohols		
Isobutanol	104	9 (20)
sec-Butanol	99	22 (20)
Amyl alcohol	130	2.6(20)
Ethers		
Ethyl ether	34	10 (10)
Ketones		
Methyl ethyl ketone	80	26 (22)
Ethers		
Ethyl formate	54	10 (18)
Methyl acetate	57	33 (22)
Ethyl acetate	77	9 (15)
Propyl acetate	101	1.9(20)
Isopropyl acetate	90	3.2(20)

The amount of the cellulose derivative employed as the wall-forming substance of the aspirin-containing capsules may be freely selected in the range of from about 1/100 to about 1/5 (by weight) of the aspirin to be dispersed in the organic solvent(s), but it is preferably from 1/50 to 1/20 the weight of the aspirin. The solution in which aspirin is dispersed is preferably one containing cellulose derivative in a concentration of from 1 to 10 wt %.

The amount of the encapsulation medium used may be from 3 to 19 times the amount of aspirin dispersed in the organic solvent, but the amount is preferably from 5 to 7 times from the viewpoint of ease of preparation and economy.

The following Examples are now offered to illustrate preferred embodiments thereof.

EXAMPLE 1

Into a solution of 1.5 g of ethyl cellulose "N-100" (Trade name) in 35 ml of ethyl acetate were dispersed 28.5 g of aspirin particles having a particle size of from 300 μ to about 50 μ. The dispersion thus obtained was added to 200 ml of aspirin-saturated water as an encapsulation medium while maintaining all components at 15°C, and the mixture was stirred to form small droplets of 300 to 500 μ in size [the aspirin; cellulose ratio was about 1:19]. By continuing the stirring, ethyl acetate was evaporated off over about 1 hour at atmospheric pressure to provide 30 g of ethyl cellulose-encapsulated aspirin. 95 Wt % of the total aspirin particles were encapsulated in walls about 1—2 μ thick: the process commonly provides walls of about 1—3 μ thick containing about 10—30 times their weight of aspirin.

1 g of the thus obtained aspirin-containing capsules was incorporated in 1 litre of artificial gastric juice at 37°C and the time required for dissolving one half of the total weight of the encapsulated aspirin was measured and was found to be 60 minutes. On the other hand, the time required for dissolving the same total amount of encapsulated aspirin was about 15 minutes.

EXAMPLE 2

Aspirin-containing capsules were obtained as in Example 1 except that a solution of 2 g of aspirin and about 20 ml of ethyl acetate in 200 g of water was used as the encapsulation medium.

WHAT WE CLAIM IS:—

1. A process of encapsulating aspirin which comprises:

1) dispersing aspirin particles in a solution of a film-forming cellulose derivative in an organic solvent partially miscible with water;

2) adding the dispersion to an encapsulation medium comprising water in which is dissolved an organic solvent which is partially miscible with water and/or aspirin;

3) stirring the mixture to form a fine dispersion of the aspirin; and

4) evaporating off the organic solvent thereby to encapsulate the aspirin particles in the cellulose derivative.

2. A process as claimed in Claim 1, wherein the cellulose derivative is an alkyl cellulose.

3. A process as claimed in Claim 2, wherein the cellulose derivative is ethyl cellulose.

4. A process as claimed in any preceding Claim. wherein the organic solvent of step 1) is miscible with water in a concentration of from 1 weight % to 35 weight %.

5. A process as claimed in any preceding Claim, wherein the cellulose derivative in step 1) is completely dissolved by the organic solvent, which contains the cellulose deriva-